On May 31, 2002, Applicants filed an executed terminal disclaimer for the above referenced patent application. Applicants herein provide a marked version of claim 48. The marked version of claim 48 was the only item on page six of the February 14, 2002 response, which page was not received by the PTO. Please enter the February 14, 2002 amendment, as well as the present response to the May 1, 2002 Office Communication.

VERSION WITH MARKINGS TO SHOW CHANGES MADE: CLAIM 48

48. (once amended) The method of claim 45, wherein the animal is a human patient infected with [a] the virus selected from the group consisting of HIV-1, HIV-2, HTLV-1, HTLV-2, hepatitis A, hepatitis B, hepatitis C, and dengue fever virus.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX

PENDING CLAIMS

1. A method of increasing the mutation rate of a virus, comprising administering an RNA nucleoside analog to a virally infected cell, wherein the analog is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the virus, said analog replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said analog complements a second nucleotide which is other than the first nucleotide, thereby inducing the virus to mutate.

2. The method of claim 1, wherein the RNA nucleoside analog replaces uracil.

3. The method of claim 1, wherein the RNA nucleoside analog replaces adenine.

4. The method of claim 1, wherein the RNA nucleoside analog replaces cytidine.

5. The method of claim 1, wherein the RNA nucleoside analog replaces guanine.

6. The method of claim 1, wherein the RNA nucleoside analog is incorporated by the polymerase into the RNA copy of the genomic nucleic acid with an efficiency at least about 0.1% that of a naturally occurring complementary nucleic acid.

7. The method of claim 1, wherein the method further includes the proviso that the RNA nucleoside analog is not ribavirin or a 5-halo analog of 1-â-D-ribofuranosylimidazole-4-carboxamide.

8. The method of claim 1, wherein the RNA analog is a non-chain terminating analog.

9. The method of claim 1, wherein the method further includes the proviso that if the virus is HIV, then the RNA nucleoside analog is not HEPT or a 2',5'-bis-O-sialylated-3'-spiro-

substituted (TSAO) adenine, hypoxanthine, N^1-alkyl-hypoxanthine, or xanthine or a nucleoside analog that is incorporated and extended at high efficiency by reverse transcriptase of HIV.

10. The method of claim 1, wherein the nucleoside analog is selected from the group consisting of N^4-aminocytidine, N^1-methyl-N^4-aminocytidine, 3,N^4-ethenocytidine, 3-methylcytidine, 5-hydroxycytidine, N^4-dimethylcytidine, 5-(2-hydroxyethyl)cytidine, 5-chlorocytidine, 5-bromocytidine, N^4-methyl-N^4-aminocytidine, 5-aminocytidine, 5-nitrosocytidine, 5-(hydroxyalkyl)-cytidine, 5-(thioalkyl)-cytidine and cytidine glycol, 5-hydroxyuridine, 3-hydroxyethyluridine, 3-methyluridine, O^2-methyluridine, O^2-ethyluridine, 5-aminouridine, O^4-methyluridine, O^4-ethyluridine, O^4-isobutyluridine, O^4-alkyluridine, 5-nitrosouridine, 5-(hydroxyalkyl)-uridine, and 5-(thioalkyl)-uridine, 1,N^6-ethenoadenosine, 3-methyladenosine, and N^6-methyladenosine, 8-hydroxyguanosine, O^6-methylguanosine, O^6-ethylguanosine, O^6-isopropylguanosine, 3,N^2-ethenoguanosine, 0^6-alkylguanosine, 8-oxo-guanosine, 2,N^3-ethenoguanosine, and 8-aminoguanosine.

11. The method of claim 1, wherein the virus is a retrovirus or a flavivirus.

12. The method of claim 11, wherein the virus is a pestivirus.

13. The method of claim 1, wherein the polymerase is a human polymerase II.

14. The method of claim 1, wherein the cell is in cell culture.

15. The method of claim 1, wherein the cell is in an animal.

16. The method of claim 1, wherein increasing the mutation rate of the virus produces a progressive loss of viability of the virus.

17. The method of claim 1, comprising administration of more than one species of RNA nucleoside analog to the virally infected cell.

18. The method of claim 1, wherein the virus is an RNA virus selected from the group consisting of hepatitis C, coronavirus, influenza, respiratory syncytial virus, BVDV, and dengue fever.

45. (once amended) A method of increasing the mutation rate of a virus in an animal comprising administering to the animal a therapeutically effective dose of a mutagenic ribonucleoside analog composition wherein the analog is one that in a infected cell with a virus of interest is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the virus, said analog replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said analog complements a second nucleotide which is other than the first nucleotide together with a pharmaceutically acceptable carrier.

46. The method of claim 45, wherein the nucleoside analog is selected from the group consisting of N^4-aminocytidine, N^1-methyl-N^4-aminocytidine, 3,N^4-ethenocytidine, 3-methylcytidine, 5-hydroxycytidine, N^4-dimethylcytidine, 5-(2-hydroxyethyl)cytidine, 5-chlorocytidine, 5-bromocytidine, N^4-methyl-N^4-aminocytidine, 5-aminocytidine, 5-nitrosocytidine, 5-(hydroxyalkyl)-cytidine, 5-(thioalkyl)-cytidine and cytidine glycol, 5-hydroxyuridine, 3-hydroxyethyluridine, 3-methyluridine, O^2-methyluridine, O^2-ethyluridine, 5-aminouridine, O^4-methyluridine, O^4-ethyluridine, O^4-isobutyluridine, O^4-alkyluridine, 5-nitrosouridine, 5-(hydroxyalkyl)-uridine, and 5-(thioalkyl)-uridine, 1,N^6-ethenoadenosine, 3-methyladenosine, and N^6-methyladenosine, 8-hydroxyguanosine, O^6-methylguanosine, O^6-ethylguanosine, O^6-isopropylguanosine, 3,N^2-ethenoguanosine, 0^6-alkylguanosine, 8-oxo-guanosine, 2,N^3-ethenoguanosine, and 8-aminoguanosine.

47. The method of claim 45, wherein the RNA nucleoside analog is incorporated by a polymerase present in virally infected cells of the animal into an RNA copy of a genomic nucleic acid of the virus with an efficiency at least about 0.1% that of a naturally occurring complementary nucleic acid.

48. (once amended) The method of claim 45, wherein the animal is a human patient infected with the virus selected from the group consisting of HIV-1, HIV-2, HTLV-1, HTLV-2, hepatitis A, hepatitis B, hepatitis C, and dengue fever virus.

49. The method of claim 45, wherein the animal is a human patient having a disease selected from the group consisting of AIDS, hepatitis B, hepatitis C, T-cell leukemia.

50. The method of claim 45, the animal having a disease selected from the group consisting of feline leukemia virus, feline immunodeficiency virus, BVDV, or vesicular stomatitis virus.

66. The method of claim 1, wherein the RNA nucleoside analog is an enantio-specific nucleoside analog.